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Palladium-Catalyzed Selective Anti-Markovnikov Oxidation of Allylic Esters**

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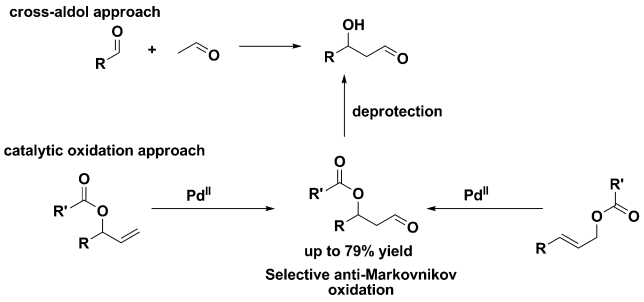
The palladium(II)-catalyzed oxidation of alkenes to carbonyl compounds, usually referred to as the Wacker or Wacker–Tsuji reaction,[1,2] is arguably one of the best-known reactions catalyzed by palladium. It is an important catalytic process industrially, for the production of ethanal, and synthetically, for the conversion of olefins to ketones.[3,4] The oxidation of terminal alkenes typically proceeds with selective formation of methylketones.[5] The anti-Markovnikov (AM) Wacker oxidation of terminal olefins to aldehydes remains, however, a major challenge.[6] Under certain conditions, AM selectivity is obtained with styrenes,[7–10] Michael-type acceptor alkenes[11] and certain olefins, such as 2-vinyl-furanosides, bearing a directing functional group.[12] Indeed, high aldehyde selectivity in the catalytic oxidation of phthalimide-protected allylic amines was reported by our group to yield a key intermediate in the preparation of β-amino acids.[13] On the other hand, Sigman and co-workers have reported the regioselective oxidation of protected allylic amines controlled by various palladium catalysts to yield the corresponding methyl ketones.[14]

In 1986, Pd^{II}-catalyzed aldehyde selective oxidation of styrene with O_2 and CuCl in *t*BuOH at 30 °C was reported by Feringa.[7] Later, Wenzel reported good selectivity (6:1) for aldehyde formation from allyl acetate (56 % combined yield of aldehyde and ketone), in *t*BuOH with $PdCl_2/CH_3CN/CuCl/NaCl$ at 50 °C.[15] More recently, the aldehyde-selective oxidation of styrenes was reported by Grubbs and co-workers using the catalyst $[PdCl_2(CH_3CN)_2]$, *p*-benzoquinone as oxidant, and *t*BuOH as solvent at 85 °C.[10] However, a more general anti-Markovnikov alkene oxidation of non-aryl alkenes under mild conditions remains a challenge, despite the tremendous value in extending this reaction to other substrate classes, in particular allylic alcohols and esters.

β-Hydroxy aldehydes are usually prepared by the cross-aldol reaction between aldehydes or an aldehyde and a ketone.[16] The direct catalytic formation of an aldehyde by selective attack at the terminal carbon of an α-olefin would be a highly valuable alternative. However, the selective anti-Markovnikov oxidation of allylic alcohols into β-hydroxy aldehydes has proven to be very difficult owing to formation of the ketone products and competing olefin isomerization.[17]

Herein, we demonstrate the aldehyde-selective catalytic oxidation of ester-protected allylic alcohols with as low as 0.5 mol % of $[PdCl_2(PhCN)_2]$ and *p*-benzoquinone (BQ) as oxidant in *t*BuOH under ambient conditions. Importantly, the same anti-Markovnikov oxidation products were obtained selectively from both branched and linear allylic esters (Scheme 1), owing to rapid isomerization between allylic esters under the reaction conditions (see below).



Scheme 1. Synthesis of β-hydroxy aldehydes by cross aldol reactions compared with Pd^{II}-catalyzed oxidation of allylic esters.

Initial attempts at AM oxidation of ester-protected allylic alcohols, under conditions used earlier by our group for the AM oxidation of phthalimide-protected allylic amines,[13] primarily provided the Markovnikov product (Supporting Information, Table S1,). A broad screening of reaction conditions (see the Supporting Information), indicated that *t*BuOH and the stoichiometric oxidant *p*-benzoquinone offered the highest AM selectivity. The methyl ketone was the main product obtained in the oxidation of unprotected allylic alcohol with $[PdCl_2(CH_3CN)_2]$ and *p*-benzoquinone in acetone/*t*BuOH (Table 1, entry 1). Protection of oct-1-en-3-ol with 2-methoxyethoxymethyl and benzyl groups did not realize an improvement in regioselectivity (Table 1, entries 2 and 4). Furthermore, the trimethylsilyl-protected allyl alcohol was found to be unstable, with deprotection observed under the reaction conditions (Table 1, entry 3).

In sharp contrast, a wide range of allylic esters were found to give good aldehyde selectivity under the present reaction conditions (Table 1, entries 5–12).[18] Aryl ester protected but-3-en-2-ol provided a $>5:1$ ratio of aldehyde to ketone (Table 1, entries 5, 6, 7, and 10). 2-Furoyl protected but-3-

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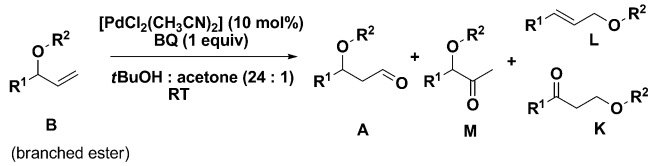
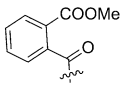
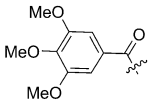
Table 1: Effects of protecting groups on the oxidation of allylic alcohols.[a]



Entry	R^1	R^2	A/M/(L+K)[b]
1[c]	C_5H_{11}	H	11:89:0
2	C_5H_{11}	MEM	15:85:0
3[d]	C_5H_{11}	TMS	–
4	Me		20:80:0
5	Me		79:14:7
6	Me		79.5:11.5:9
7	Me		75:13.5:11.5
8	Me		83:11:6
9	Me		85:10:5
10	Me		74.5:13.5:12
11	C_5H_{11}		87:6:7
12	C_5H_{11}		86:7:7

[a] Reactions were performed with a substrate concentration of 0.025 M and the reaction mixtures were stirred at RT until completion was indicated by TLC, unless otherwise stated. All reactions gave full conversion, as determined by ^{1}H NMR spectroscopy. [b] Selectivity determined by ^{1}H NMR spectroscopy. [c] Unidentified side products observed. [d] Deprotection was observed under the reaction conditions. **A** = anti-Markovnikov product, **M** = Markovnikov product, **K** = ketone product from oxidation of linear ester, **L** = linear ester, MEM = β-methoxyethoxymethyl ether, TMS = trimethylsilyl.

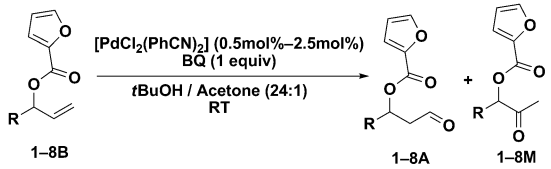
en-2-ol and oct-1-en-3-ol gave a >7:1 ratio of aldehyde and ketone (Table 1, entries 8 and 11). Similar aldehyde selectivity was obtained using the thiophene-2-carboxyl and acetyl protecting groups (Table 1, entries 9 and 12). The 2-furoyl protecting group provided high selectivity for the aldehyde products and was focused upon in the optimization of reaction conditions (Tables S3, S4, and S5).

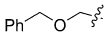
Although the selectivity was not affected significantly when water was present in near stoichiometric amounts, the addition of excess water led to a reduction in selectivity (Table S3). The solidification of *t*BuOH at ambient temperatures was found to be problematic and, although the use of higher temperatures (Table S3) avoided this, the selectivity was also reduced. The solidification of *t*BuOH could be conveniently avoided by the addition of cosolvents, other than water, such as acetone, dichloromethane, diethyl ether, and pentane (Table S6), with acetone giving the highest selectivities (Table S3, entry 5b). The use of high substrate concentrations (0.5 M), together with the fact that water does not need to be added to the reaction indicates, tentatively, that the *t*BuOH solvent is the source of the oxygen in the aldehyde and ketone products.

A range of palladium complexes were tested for anti-Markovnikov selectivity under optimized reaction conditions (Table S2). The complex $[PdCl_2(PhCN)_2]$ showed higher selectivity in the oxidation of **2B** into the corresponding aldehyde **2A** (Table S2) and shorter reaction times in general compared with, for example, $[PdCl_2(CH_3CN)_2]$.[19]

A key challenge in the palladium-catalyzed oxidation of alkenes is the often high catalyst loadings employed.[1,3] In the present system, as little as 0.5–2.5 mol% catalyst is sufficient, providing excellent aldehyde selectivity (A/M ratios were 7:1–20:1) when substrate concentrations of 0.1–0.5 M in *t*BuOH/acetone are used (Table 2). Allylic alcohols protected with a 2-furoyl group (**1**–**8B**) were tested under the optimized reaction conditions: $[PdCl_2(PhCN)_2]$ (0.5–2.5 mol%), *p*-benzoquinone (1 equiv) and *t*BuOH/acetone (24:1 v/v) at room temperature (Table 2).

Table 2: Pd^{II}-catalyzed oxidation of branched allylic esters.[a]



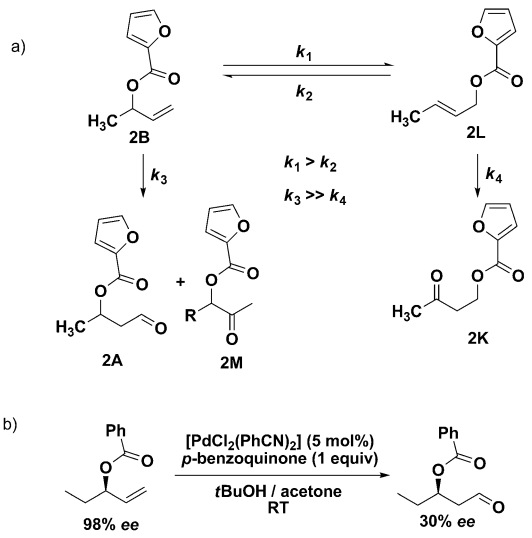
Entry	R	B	Conv.	A/M	A	Yield [%][b]
1[c]	H	**1B**	full	11:1	**1A**	78
2[d]	CH_3	**2B**	full	7:1	**2A**	71
3[d]	C_2H_5	**3B**	full	20:1	**3A**	79
4[e]	C_5H_{11}	**4B**	full	20:1	**4A**	73
5[e,f]		**5B**	95%	20:1	**5A**	45
6[c]		**6B**	full	20:1	**6A**	71
7[e,f]	Ph	**7B**	full	20:1	**7A**	52
8[e,g]	Bn	**8B**	95%	20:1	**8A**	64

[a] Reactions were performed on 1 mmol of substrate, with a substrate concentration of 0.5 M, unless otherwise noted. Conversion and selectivity were determined by ^{1}H NMR spectroscopy. Reaction mixtures were stirred at RT until completion, as determined by TLC analysis. [b] Yield of isolated product. [c] $[PdCl_2(PhCN)_2]$ (0.5 mol%). [d] $[PdCl_2(PhCN)_2]$ (1 mol%). [e] $[PdCl_2(PhCN)_2]$ (2.5 mol%). [f] Unless otherwise stated, the major side product was the corresponding linear allylic ester (see the Supporting Information). [g] 0.1 M substrate concentration. Bn = benzyl.

Most aliphatic allylic esters underwent oxidation with high selectivity for the formation of aldehydes in >70% yield (Table 2, entries 1–4). Ester-protected 4-methylhex-1-en-3-ol (**5B**) also provided good selectivity, albeit in a yield of only 45% of aldehyde **5A**, owing to the formation of the corresponding linear allylic ester **5L** (Table 2, entry 5 and see below).

In contrast, the benzyl methyl ether substituted allylic ester provided high selectivity and yield of the aldehyde product (Table 2, entry 6). The phenyl- and benzyl-substituted allylic esters provided the aldehyde in slightly lower yield (52% and 64%; Table 2, entries 7 and 8, respectively); again primarily owing to rearrangement, not ketone formation (see below).

When *p*-benzoquinone was omitted from the reaction mixture, the linear allylic ester (for example, **2L**) was the main species present within several minutes (Scheme 2). This



Scheme 2. a) Isomerization equilibrium and oxidation of linear and branched alkenes. The mechanism is consistent with b) the partial loss of *ee* in the benzyl-protected substrate and the conversion of linear allylic esters (such as **2L**) into branched ester-protected β-hydroxy aldehydes (Table 3).

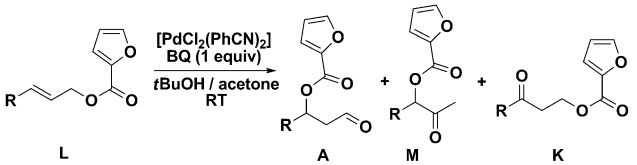
indicates that it is the thermodynamically most stable regioisomer and that, under the reaction conditions, an equilibrium (for example, between **2B** and **2L**) is established. Such a rearrangement, catalyzed by palladium, has been noted previously by Henry, Oehlschlager, and others.[20] In the presence of *p*-benzoquinone, the rearrangement also occurred, but was slower (ca. 30 min).[26,27] Using the (*S*)-enantiomer of benzoate-protected pent-1-en-3-ol,[21] the anti-Markovnikov product, which was obtained with 30% *ee*, (Scheme 2b), showed partial retention of configuration. This indicated that the rate of oxidation was of a similar order of magnitude as the rate of isomerization to the corresponding linear allylic ester (Scheme 2).

From a mechanistic perspective, the rearrangement could suggest the involvement of (π-allyl)-palladium complexes. However, in the presence of deuterated acetic acid, neither the oxidized nor the rearrangement products of an acetyl-protected allylic ester contained the $CD_3C(=O)-$ moiety.[22]

Importantly, despite the relatively rapid reversible rearrangement to the linear allylic ester, in the presence of *p*-benzoquinone, all substrates examined gave the branched aldehyde as the main product under optimized reaction conditions. This, together with the low amounts of the ketone (**2K**), which result from oxidation of the linear allylic ester, indicates that $k_3 \gg k_4$ and that the Curtin–Hammett principle[23] applies (Scheme 2).

The observation of isomerization predominantly to the linear isomer under the reaction conditions encouraged us to examine the possibility of using linear allylic esters as starting material to obtain protected β-hydroxy aldehydes **A**. Indeed, several examples of linear esters **L** (Table 3) demonstrated

Table 3: Oxidation of linear allylic esters.

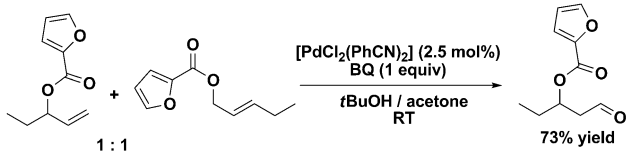


Entry	R	L	Conv.[a,b]	A/M	A	Yield [%][b]
1[c]	CH_3	**2L**	full	7:1	**2A**	70
2[d]	C_2H_5	**3L**	full	16:1	**3A**	74
3[d]	C_5H_{11}	**4L**	95%	15:1	**4A**	72
4[c]		**6L**	full	20:1	**6A**	71
5[e,f]	Bn	**8L**	85%	10:1	**8A**	43

[a] Reactions were performed on 1 mmol of substrate, with a substrate concentration of 0.5 M. Conversion and selectivity were determined by ^{1}H NMR spectroscopy. Reaction mixtures were stirred at RT until completion, as determined by TLC analysis. [b] Yield of isolated product. [c] $[PdCl_2(PhCN)_2]$ (2.5 mol%). [d] $[PdCl_2(PhCN)_2]$ (1 mol%). [e] $[PdCl_2(PhCN)_2]$ (10 mol%). [f] 0.1 M substrate concentration.

that this alternative substrate class could be used, with selectivities and yields essentially the same as those obtained from the corresponding branched allylic esters (Table 3). An exception was 2-furoyl protected 3-phenyl-prop-2-ene-ol **8L**, which showed lower conversion and yield, and which required higher catalyst loadings than the corresponding branched allylic ester **8B**.

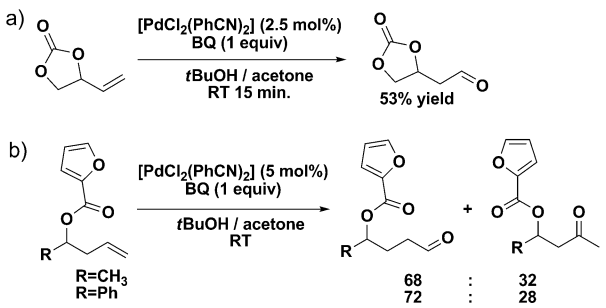
A major advantage of the isomerization between branched and linear allylic esters is that even substrate mixtures provide only a single major product, that is, the aldehyde, in this Pd^{II}-catalyzed oxidation (Scheme 3).



Scheme 3. Oxidation of a mixture of linear and branched allylic esters.

The ester group at the allylic position of the alkenes was found to be key to the anti-Markovnikov selectivity when compared with other protecting groups (Table 1). This protecting-group class was previously found to also be important in the rearrangement of allylic esters with palladium(II) complexes.[20] However, we have found that the rearrangement can be blocked by the use of cyclic protecting groups, for example with 4-vinyl-1,3-dioxolan-2-one, where

the corresponding aldehyde was obtained with high selectivity along with only trace ketone formation and no observed rearrangement (Scheme 4a). Furthermore, the reaction pro-



Scheme 4. Oxidation of 4-vinyl-1,3-dioxolan-2-one and homoallylic esters.

ceeded at a much faster rate than with acyclic allylic esters, possibly owing to the absence of the competing rearrangement. In this case, competing decarboxylation[28] was also observed, which leads to decreased yield. It is notable that, as for isomerization, decarboxylation is much faster in the absence of *p*-benzoquinone.

Finally, the AM selectivity observed for homoallylic esters, which cannot undergo isomerization to the linear allylic esters, was found to be surprisingly high under the optimized reaction conditions for allylic esters (Scheme 4b).

In summary, we have developed the first highly selective catalytic anti-Markovnikov oxidation of allylic esters, which provides a facile route to the synthesis of protected β-hydroxy aldehydes from terminal alkenes with high selectivity, high yield, and, importantly, with low Pd catalyst loadings. Furthermore, the aldehyde products can be obtained using either the branched or linear protected allylic esters under the same reaction conditions, which provides a new synthetic approach for the preparation of β-hydroxy aldehydes from linear allylic esters, or even mixtures of terminal and internal alkenes. Future studies will focus on the catalytic use of *p*-benzoquinone using a redox coupling with oxygen approach,[24] as applied recently in the Pd-catalyzed oxidation of internal alkenes.[25]

Experimental Section

General procedure for the catalytic oxidation of branched allylic esters (Table 2): $[PdCl_2(PhCN)_2]$ and *p*-benzoquinone were dissolved in a mixture of *t*BuOH and acetone (24:1 v/v). The branched allylic ester **B** (0.5 M) was added to the mixture under N_2 and stirred at room temperature until the reaction was complete, as indicated by TLC analysis. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica-gel chromatography yielded the desired aldehyde **A**.

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Keywords: allylic esters · anti-Markovnikov · benzoquinone · oxidation · palladium

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[18] Although the anti-Markovnikov oxidation products of the branched allylic esters were the major products, other products, including Markovnikov oxidation products, rearrangement to the linear allylic esters, and the oxidation product of the linear allylic ester were obtained (Table 2, entries 1–8).
[19] Several other palladium complexes, such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ provided no conversion (see also Table S2), whereas $PdCl_2$ primarily provided the linear allylic ester (**L**). Oxidants, other than benzoquinone (Table S4), and other solvents (Table S1 and S5) provided lower reactivity and selectivity.
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